UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE:

MIRENA IUS LEVONORGESTREL-RELATED PRODUCTS LIABILITY LITIGATION (NO. II)

17-MD-2767 (PAE)
17-MC-2767 (PAE)

This Document Relates To All Actions

PLAINTIFFS' MEMORANDUM OF LAW IN SUPPORT OF OMNIBUS MOTION TO EXCLUDE GENERAL CAUSATION EXPERT TESTIMONY OF DEFENDANTS' EXPERT WITNESSES

TABLE OF AUTHORITIES

Cases

Other Authorities

Scientific Literature

TABLE OF CONTENTS

I. Introduction

None of Bayer's twelve experts apply a reliable methodology to assess whether Mirena is capable of causing or contribution to intracranial hypertension ("IH"). Instead, they conjure up identical excuses, with the same sources, analyses, and language for *not* weighing the peer-reviewed literature and scientific data. None of Bayer's experts disclosed their assignments, and they present their opinions as a cross-examination: literature and data supporting a causal association is picked apart at length, with hypothetical, speculative, and conjectural limitations of the data elevated to conclusive refutations. Even studies that would, under any rational interpretation, present mixed evidence are deemed wholly unreliable for purposes favoring the Plaintiffs yet incontrovertible for purposes favoring Bayer.

Most of the claims made by Bayer's experts *should* be quantitative—for example, the extent of "preferential prescribing" of Mirena to obese women, or the expected rate of intracranial hypertension among Mirena users—but Bayer's experts steadfastly refuse to explain or to quantify their sweeping conclusions, preferring instead to rely on subjective determinations as their basis for rejecting objective data.

Bayer's experts universally renounce the very notion of a plausible biological mechanism on purely semantic grounds, refusing to even consider the vast body of literature and data in support of Plaintiffs' conclusions. Bayer's experts are categorically unqualified to rebut Plaintiffs' world-class experts in CSF regulation, pathophysiology of intracranial hypertension, and steroidal contraceptive pharmacokinetics, and Bayer's experts all either fail to actually confront Plaintiffs' expert opinions or do so in a cursory, piecemeal fashion.

Individually and collectively, Bayer's experts suffer numerous methodological shortcomings and logical errors in the application of unfounded assumptions. Their opinions are unreliable and inadmissible under Rule 702 and *Daubert*.

II. Standard of Review

This Court is well-acquainted with *Daubert*,[1] so a full recitation is unnecessary.

A. The Scientific Daubert's Four Factors Are Well-Suited To Epidemiological, But Not Pathophysiological, Opinions

The Court must ensure that expert testimony "is not only relevant, but reliable," *Daubert*, 509 U.S. at 589, and "reliability within the meaning of Rule 702 requires a sufficiently rigorous analytical connection between that methodology and the expert's conclusions." *Nimely*, 414 F.3d at 396. But it is less clear when and how the four factors outlined by *Daubert*[2] should apply. The *Daubert* factors "may or may not be pertinent in assessing reliability, depending on the nature of the issue, the expert's particular expertise, and the subject of his [or her] testimony." *Kumho Tire Co*., 526 U.S. at 150 (internal quotes omitted). The majority of scientific testimony in this case is, in a broad sense, either epidemiological[3] or pathophysiological.[4] The epidemiological testimony relates to, *e.g.*, the distribution of obesity among Mirena users and the effect of potential confounding in studies of intracranial hypertension—subjects discussed by virtually every expert. The pathophysiological testimony relates to, *e.g.*, the biological effects of levonorgestrel and the mechanisms of intracranial hypertension—subjects also discussed by virtually every expert.

Plaintiffs submit the *Daubert* factors are useful when assessing the experts'

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[1] *LVL XIII Brands, Inc. v. Louis Vuitton Malletier S.A.*, 209 F.Supp.3d 612 (S.D.N.Y., 2016).

[2] That is, (1) whether the expert's technique or theory can be or has been tested; (2) whether it has been subjected to peer review and publication; (3) whether there is a high error rate for the expert's technique, and whether there are standards controlling the technique's operation; and (4) whether the expert's technique or theory is generally accepted by the relevant scientific community. 509 U.S. at 592-94.

[3] Per Oxford English Dictionary, relating to "the incidence, distribution, and control of diseases."

[4] Per Oxford English Dictionary, relating to "the disordered physiological processes associated with disease or injury."

epidemiological opinions but not when assessing the experts' *pathophysiology* opinions. Epidemiological methods, such as Bradford Hill, reaching conclusions about the prevalence of obesity among Mirena users (or about the extent of Mirena use among a population), or calculating the effect of a potential confounding variable on a case-control study, all have some degree of "error rate" and "standards controlling the technique's operation." For example, several experts create "2x2" tables to calculate odds ratios, which the Court can do itself using the same tool most of the experts used.[5] The majority of experts discuss selection of cases and controls in case-control studies, an issue for which there is literature designed to help "the uninitiated."[6]

Pathophysiological methods in the context of intracranial hypertension, however, are not easily evaluated by testing or error rates, not least because the typical forms of scientific "testing" would be unethical. It would be unethical to create a study with the objective of causing intracranial hypertension or to "re-challenge" a patient with a particular medication to see if their IH recurred. As one example of the methodology used within the field of intracranial hypertension, "the following criteria should be met to include the disease or drug within [a] list of causally related associations: at least two cases should have been described; the reported cases should have met all the criteria for the diagnosis of idiopathic intracranial hypertension; and intracranial dural sinus thrombosis should have been ruled out with reasonable certainty."[7] This

[5] See http://openepi.com/TwobyTwo/TwobyTwo.htm

[6] See British Medical Journal, *Epidemiology for the uninitiated*, specifically Chapter 8: http://www.bmj.com/about-bmj/resources-readers/publications/epidemiology-uninitiated/8-case-control-and-cross-sectional

[7] Bhatt UK, et al. A 43-year-old woman on triptorelin presenting with pseudotumor cerebri: a case report. Journal of Medical Case Reports. 2012;6:122, applying method outlined by Radhakrishnan K, et al. Benign intracranial hypertension (pseudotumor cerebri). Descriptive epidemiology in Rochester, Minn, 1976 to 1990. Arch Neurol. 1993;50(1):78–80.

method is obviously "subjected to peer review and publication" and "generally accepted by the relevant scientific community," and so it is reliable, but the method leaves little room for "testing" or assessing an "error rate." A rigid application of the *Daubert* factors could result in a wrongful preclusion of it or of similar methods relating to pathophysiological testimony.

B. Methods That Cannot Be Objectively Challenged Are Inherently Suspect

In the prior Mirena MDL, the Court noted, "when an expert is offering testimony that is presented as a scientific conclusion and the expert's method fails to satisfy any of the factors identified in *Daubert*, a court should pause and take a hard look before allowing a jury to consider it."[8] Plaintiffs do not see how this standard can be applied in practice—for example, *all* experts deserve a "hard look," regardless of whether or not they satisfy the *Daubert* factors, because an expert's opinion is inadmissible if it "is connected to existing data only by the *ipse dixit* of the expert," for a "court may conclude that there is simply too great an analytical gap between the data and the opinion proffered." *Joiner*, 522 U.S. at 146. Plaintiffs prefer the formulation this Court adopted in *Louis Vuitton*, which applied additional scrutiny when it appeared an expert's "methodology has not been—and, for multiple reasons, cannot be—tested or challenged in any objective sense." 209 F.Supp.3d at 644.

C. Inconsistent Approaches To Scientific Evidence Is A Sign Of Unreliability

As the Third Circuit elaborated:

> The specific way an expert conducts such an analysis must be reliable; all of the relevant evidence must be gathered, and the assessment or weighing of that evidence must not be arbitrary, but must itself be based on methods of science. To ensure that the Bradford Hill/weight of the evidence criteria is truly a methodology, rather than a mere conclusion-oriented selection process there must be a scientific method of weighting that is used and explained. For this reason, the specific techniques by which the weight of the evidence/Bradford Hill methodology is conducted must

[8] *In re Mirena Iud Prods. Liab. Litig.*, 169 F.Supp.3d 396, 430 (S.D.N.Y., 2016)(quoting *In re Methyl Tertiary Butyl Ether (MTBE) Prods. Liab. Litig.*, 593 F.Supp.2d 549, 564 (S.D.N.Y.2008).

themselves be reliable according to the principles articulated in *Daubert*.

In re Zoloft, 858 F.3d 787, 796 (3d Cir., 2017)(internal citations and quotations omitted). In other words, "the 'techniques' used to implement the analysis must be 1) reliable and 2) reliably applied." *Id.* Of course, "[t]he trial court has latitude in deciding how to test an expert's reliability."[9] The analysis is, in many ways, common sense. For example, an expert "cannot have it both ways and produce a reliable opinion under Rule 702,"[10] such as by selectively applying arguments to some evidence but not other evidence, [11] and an expert cannot "ignore directly relevant scientific data in violation of his [or her] own standards."[12]

D. Speculative Opinions Unsupported By The Data Must Be Precluded

As this Court recognized in *Louis Vuitton*,

> "In addition to setting forth these criteria for testing an expert's methodology, the Supreme Court has also stated that reliability within the meaning of Rule 702 requires a sufficiently rigorous analytical connection between that methodology and the expert's conclusions." *Nimely*, 414 F.3d at 396. "[N]othing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence which is connected to existing data only by the ipse dixit of the expert." *Gen. Elec.*, 522 U.S. at 146, 118 S.Ct. 512. Accordingly, "expert testimony should be excluded if it is speculative or conjectural," *Boucher*, 73 F.3d at 21, or where the proffered opinion is "based on data, a methodology, or studies that are simply inadequate to support the conclusions reached," *Amorgianos*, 303 F.3d at 266.

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[9] *Figueroa v. Boston Scientific Corp.*, 254 F.Supp.2d 361 (S.D.N.Y., 2003).

[10] *In re Lipitor Prods. Liab. Litig.*, 185 F.Supp.3d 761, 780 (D.S.C., 2016), citing *In re Rezulin Products Liab. Litig.*, 309 F.Supp.2d 531, 563 (S.D.N.Y.2004) ("[The expert's] selectivity in defining the universe of relevant evidence thus violated his own standard of proper methodology.")

[11] *Miller v. Pfizer, Inc.*, 196 F.Supp.2d 1062, 1072 Fn 25 (D. Kan., 2002)("… Pfizer cites no evidence which suggests a relevant difference between Zoloft and other SSRI drugs. Indeed in some instances Pfizer insists that because Zoloft is similar to other SSRI drugs, it—like the other SSRI drugs—does not cause suicide. … Obviously Pfizer cannot have it both ways.")

[12] *In re Rezulin Products Liab. Litig.*, 309 F.Supp.2d 531, 563, Fn 146 (S.D.N.Y.2004)("While as a general proposition plaintiffs are correct that neither rule 702 nor Daubert requires experts to rely on epidemiological data, the dispositive fact here is that Dr. Gale pointedly ignored directly relevant scientific data in violation of his own standards.")

209 F.Supp.3d at 644. To be sure, "no one denies that an expert might draw a conclusion from a set of observations based on extensive and specialized experience," *Kumho Tire Co.* at 156, but the expert must still "employ[ ] in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field," *id.* at 152. The Court's prior formulation, i.e., looking to whether the methodology and analysis can be "challenged in any objective sense," is a prudent and appropriate approach supported by the case law. To put it another way, when assessing whether an expert uses a reliable methodology to reach a particular conclusion, is it possible to follow the expert's steps, confirm their conclusion, and challenge the various steps along the way?

III. Defendants' Experts Have No Discernable Methodology, Nor Do They Apply A Reliable Methodology To Issues Relevant To General Causation

The opinions offered by Bayer's experts do not meet any of the *Daubert* factors:

(1) Bayer's experts do not identify even their *assignments*, much less identify and then apply a tested technique or theory to assess whether the levonorgestrel in Mirena is capable of causing or contributing to IH.

(2) Neither the experts' methods nor the conclusions they reach with those methods have been subject to peer review and publication. Instead, Bayer's experts use arguments developed for litigation to disregard peer-reviewed publications.

(3) There is no error rate nor method for controlling for their techniques. Bayer's experts refused to use quantitative methods to test their theories and refused to quantify their conclusions. For example, all of Bayer's experts rely heavily on the possibilities of "preferential prescribing" and "confounding by indication," yet not one expert attempted to quantify the extent of "preferential prescribing" and not one expert attempted to calculate the effect "confounding by indication" would have on the literature and data showing a causal association between levonorgestrel and IH.

(4) Their techniques are contrary to those accepted by the community researching IH, which is how Bayer's experts repeatedly reach conclusions at odds with the literature, such as denying the role of sex hormones in causing IH[13] and denying associations between IH and growth hormone, tetracyclines, and retinoids.[14]

[13] See § VI, *infra*.

[14] *Compare* UpToDate, Idiopathic intracranial hypertension (pseudotumor cerebri): Epidemiology

See § II(A), *supra*, and *cf. Daubert*, 509 U.S. at 592-94.

Similarly, it is impossible to test or challenge the methods used by Bayer's experts in any objective sense. *See* § II (B), *supra*. Bayer's experts never identify what method they are using; never identify how they weigh evidence; adopt wholesale the literature, analysis, and conclusions of Bayer's signal assessments without addressing the limitations of those sources or contrary data, such as the data in Bayer's own signal detection database; never address the literature cited by Plaintiffs' experts; raise myriad conjectural objections to the literature about levonorgestrel and IH but never mention, much less evaluate with a reliable method, the limitations of the literature they themselves rely upon for opinions they use to justify disregarding peer-reviewed literature; use sparse and inconclusive literature to reach, without explanation, sweeping conclusions about issues key to their opinions such as "preferential prescribing" and "confounding by indication;" make no effort to quantify the extent of "preferential prescribing" nor the effect of "confounding by indication;" fail to identify any literature supporting their method for "correcting" Valenzuela 2017 by arbitrarily changing the data contained in that peer-reviewed publication; and, fail to explain the methods used to calculate their "corrections" to Valenzuela 2017.

One consequence of the lack of a methodology is the mind-numbing similarity of Bayer's experts' reports: the five neuro-ophthalmology reports are interchangeable in the literature cited, analyses, and conclusions; the three OB/GYN reports are similarly interchangeable in their literature, analysis, and conclusions; and, the three epidemiologists all adjusted the Valenzuela data in the exact same way Bayer did, making the same unexplained leaps in logic and mathematics that Bayer did, leaps they were unable to justify at deposition.

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and pathogenesis, identifying "growth hormone, tetracyclines, and retinoids" as associated with IH.

To the extent Defendants have a "methodology" independent from simply copying Bayer's own signal assessments, that "methodology" is to invent reasons to *avoid* weighing the existing literature and data. Dr. Cestari, for example, raises a variety of hypothetical objections to Valenzuela 2017, makes no effort to explain how those objections could have changed the results, then uses his own *ipse dixit* rejection of Valenzuela 2017 to justify why he performed only a cursory examination of the **mechanism** described by Plaintiffs' experts, claiming, "[m]ost importantly, the plaintiffs' experts have no reliable clinical data that supports their various mechanism theories." *Report of Dr. Cestari*, p. 21. Such a "method"—rejecting clinical data and then using his own rejection of *clinical* data as a basis for not evaluating the *mechanism*—is not just putting the cart before the horse, it is putting the horse in the cart. It is only through this sort of circular reasoning, and through the absence of any methodology, that Dr. Cestari can reach absurd conclusions such as "there is absolutely no credible evidence of a causal relationship in the medical literature," *id.* at p. 22, testimony clearly geared more towards supporting Defendants' *Daubert* motions than in assessing general causation.[15]

Dr. Cestari is not alone. Several of Defendants' experts use their *ipse dixit* rejection of Valenzuela 2017 as an excuse for not rigorously applying Bradford Hill.[16] According to these experts, Bradford Hill cannot be used until an epidemiological study free from any conceivable limitations has shown a statistically significant increase in the risk. Thus, these experts claim,

[15] The reports of Bayer's experts are riddled with similar conclusions aimed at providing fodder for their *Daubert* motions. These opinions are inadmissible. *Nimely v. City of New York*, 414 F.3d 381, 397 (2d Cir.2005)(prohibiting testimony intended to "usurp either the role of the trial judge instructing the jury as to the applicable law or the role of the jury in applying that law to the facts before it.")

[16] See, e.g., *Report of Dr. Hewitt*, p. 24; *Report of Dr. Van Stavern*, p. 15; *Report of Dr. Barnhart*, p. 57; *Report of Dr. Dinkin*, p. 13; *Report of Dr. Langer*, p. 9; *Report of Dr. Lee*, p. 5; and *Report of Dr. Dalton*, p. 27.

because they have refused to use Valenzuela 2017 at all in their analysis, they are excused from rigorously applying the Bradford Hill factors. There are three problems with this supposed "method:" Sir Bradford Hill personally rejected reliance upon "tests of significance" *in the same article cited by Defendants' experts*,[17] Defendants' experts were unable to identify any literature anywhere supporting this interpretation of Bradford Hill, and, federal courts have consistently rejected the need for an epidemiological study with a statistically significance result to establish causation.[18] Indeed, when one of Bayer's experts was questioned on this supposed rule of Bradford Hill, he abandoned it, admitting Bradford Hill can be applied even where the association is "not necessarily statistically significant," where it was seen in "disproportionate adverse event reporting," or in "consistent reports in case series," or in "consistent reports in small population studies." *Deposition of Dr. Langer,* 172:6-174:1. There can be no doubt of all of these criteria are met; Dr. Langer himself admitted the "disproportionate adverse event reporting" shown by Bayer's own database, which he was not provided by Bayer, was consistent with a causal association. See § V(D), *infra.* Thus, even assuming Bayer's experts have a reliable method for rejecting Valenzuela 2017 entirely (which they do not), the experts are *still* obliged to

[17] "None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question – is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect? No formal tests of significance can answer those questions. Such tests can, and should, remind us of the effects that the play of chance can create, and they will instruct us in the likely magnitude of those effects. Beyond that they contribute nothing to the 'proof' of our hypothesis. … [F]ar too often we deduce 'no difference' from 'no significant difference'. Like fire, the $\chi 2$ test is an excellent servant and a bad master."

[18] See *In re Zoloft*, 858 F.3d at 793 ("A causal connection may exist despite the lack of significant findings, due to issues such as random misclassification or insufficient power."). See also *Wendell v. GlaxoSmithKline*, 858 F.3d 1227, 1236 (9th Cir., 2017)("The district court also wrongfully required that the experts' opinions rely on animal or epidemiological studies. Neither are necessary for an expert's testimony to be found reliable and admissible.")

apply the Bradford Hill factors in a rigorous fashion, which they admittedly did not do.

The above examples are representative, not comprehensive. All of Bayer's experts failed to apply a consistent, reliable approach in assessing causation, rendering their opinions on causation inadmissible. *See* § II (B) & (C).

IV. Defendants' Experts Apply Entirely Different Methods When Interpreting Literature That *Supports* A Causal Association As Compared To Literature They Claim Does *Not* Support A Causal Association

An expert must "employ[ ] in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field," *Kumho Tire Co.* at 156. Here, Bayer's experts did not apply any degree of intellectual rigor even when interpreting a single paper. For example, Bayer's experts explain at length the flaws in *the first half* of the Etminan 2015 paper, then accept without question or comment and rely upon *the second half* of the Etminan 2015 paper, without addressing how one of Bayer's own consulting experts said in a published letter to the editor that the second methodology was "even more egregious than in the first methodology." Bayer's experts take this same Jekyll-and-Hyde approach with all of their opinions: conjectural objections to peer-reviewed publications supporting a causal association are presumed to render the publications wholly invalid, but, when relying on publications or data to support their arguments, Bayer's experts make no effort whatsoever to address their limitations. In many cases, the experts provide nothing more than a string of citations to support key points.

A. Bayer's Experts Wholly Reject Half Of Etminan 2015 Then Embrace, Without Explanation, The "Even More Egregious" Half

Etminan 2015 had two parts: an analysis of the FDA's FAERS database which found "increased reporting of ICH events with Mirena," and an analysis of the IMS LifeLink claims database which found "the risk of EE-norgestimate, an oral formulation, is comparable with that

with [Mirena]," and "compared with [Mirena], EE-norethindrone is protective for ICH." In response, Dr. Deborah Friedman, a neuro-ophthalmologist retained as an expert for Bayer,[19] sent a letter to the editor that noted the search terms used for the FAERS analysis were "nonspecific and often relate to other disorders," such as cerebral edema, and that the search terms used for the IMS LifeLink analysis "were even more egregious than in the first methodology," and that the IMS LifeLink analysis included multiple timing errors that would have captured patients with IH but not Mirena and vice versa.

Etminan 2015 is, at best, problematic, and it was criticized in the literature as such. An expert who was employing the same level of intellectual rigor in the courtroom as in their field would consider these problems and then either reduce the weight of Etminan 2015 in their analysis or disregard it entirely. Defendants' experts all did something different: for the FAERS analysis, the Defendants' experts adopted Dr. Friedman's criticisms wholesale and rejected that part entirely, but, for the IMS LifeLink analysis, Defendants' experts ***adopted it entirely and explicitly relied upon it*** without addressing ***any*** of Dr. Friedman's criticism or any other limitations. For example, Dr. Newman opined:

> Importantly, in their analysis of claims data, these authors found no significant difference in the frequency of 'intracranial hypertension' between patients using Mirena versus two other contraceptive medications, which does not support a causal relationship between Mirena and intracranial hypertension.

Report of Dr. Newman, p. 9. Dr. Newman is simply wrong: Etminan 2015 did *not* consider "the frequency of 'intracranial hypertension' between patients using Mirena versus two other contraceptive medications" but rather improperly considered the frequency of a variety of

[19] Dr. Friedman has never produced a report in any Mirena litigation. Such is not surprising: before she was retained by Bayer, she wrote about the "well established relationship between PTC and levonorgestrel-releasing implants." See § IV(B).

conditions, including several unrelated to IH. As Dr. Friedman's Letter to the Editor explained, "[s]earch terms for this analysis were even more egregious than in the first methodology, including obstructive hydrocephalus as well as cerebral edema, conditions which are unrelated to using hormonal contraceptives and distinct entities from PTCS," and the analysis included a host of timing problems so that, for example, prescriptions of contraceptives were considered up to 2013 but medical events were only considered up to 2012.

The failure by Dr. Newman to address Friedman 2016's criticisms makes her opinions on this issue doubly-inadmissible, both for failing to review the literature in a consistent, rigorous manner, *see* § II(C), and for the failure to consider contrary literature.[20] Moreover, because Dr. Newman considered her own unreliable conclusions about Etminan 2015 to be "important," and as part of the evidence that "does not support a causal relationship between Mirena and intracranial hypertension," the unreliability extends to her opinions about a causal relationship.

Dr. Newman is not alone: all of Bayer's neuro-ophthalmologists, OBGYNs, and epidemiologists applied the exact same analysis, relying on Dr. Friedman's criticisms to reject *the first half* of Etminan 2015 entirely but then ignoring Dr. Friedman's criticisms about *the second half* and relying on *that* component as critical support for their overall conclusions about a causal association. This inexplicable failure to evaluate *even a single study* in a reliable manner undermines all of their opinions, and the uniform manner of this failing raises questions about whether Bayer's experts are providing opinions or simply serving as a platform for their client.

B. Bayer's Experts Do Not Weigh The Norplant Evidence When Assessing A Causal Relationship Between Levonorgestrel and IH; Instead, They Ignore It Entirely

[20] Cf. *In re Rezulin Prods. Liab. Litig.*, 309 F.Supp.2d 531, 563 (S.D.N.Y.2004) (discussing problems of admissibility when expert failed to consider two epidemiological studies addressing topic at hand that reached different conclusions from expert).

Prior to the filing of Mirena IH cases, researchers in the field had no trouble concluding there was a relationship between Norplant and IH, such as neuro-ophthalmologist Dr. Deborah Friedman, who wrote in 2005: "there is a well established relationship between PTC and levonorgestrel-releasing implants. Headache is a common adverse effect of levonorgestrel; patients developing headaches or visual disturbances while using it should be evaluated for funduscopic evidence of PTC."[21] Thus, even Bayer's experts must concede "[i]mplantable contraceptives have also been associated with IIH." *Report of Dr. Van Stavern*, p. 8.

An expert using a *reliable* methodology for evaluating whether levonorgestrel is capable of causing IH would weigh the Norplant evidence accordingly. Defendants' experts, however, use a sleight-of-hand to disregard it entirely. For example, Dr. Van Stavern speculates the authors mistakenly diagnosed IH and papilledema,[22] notes that all of the patients in Wysowski 1995 were obese (thereby *also* making his analysis of Norplant dependent upon his speculative, subjective opinion that obesity irredeemably confounds all studies of IH, an issue discussed in § V(A), *infra*), asserts without elaboration that "no clear de-challenge pattern was discernible," and then concludes "the available evidence does not ***establish*** a causal relationship [between Norplant and IH]." Van Stavern, pp. 8-9 (emphasis added).

Dr. Van Stavern's approach to this issue is representative of all of Bayer's experts, raising three independent problems. First, Dr. Van Stavern demands far more from literature

[21] Friedman DI. Medication-induced intracranial hypertension in dermatology. Am J Clin Dermatol 2005;6:29–37. This article remains a standard text in the field, and it is cited by several of the studies Defendants' experts rely on, such as Daniels 2007.

[22] Dr. Van Stavern claims, "[i]n the vast majority of cases, there is inadequate documentation of whether these patients met current criteria for the diagnosis IIH, as well as whether papilledema persisted or resolved after discontinuation of the drug (or even whether it was present at all)" without elaborating upon what further "documentation" might convince him and implicitly admitting that *some* of the cases indeed had "adequate documentation."

about Norplant and IH than he does from literature about IH and weight gain or literature about obesity and Mirena use; for the former, he raises hypothetical limitations as a justification for disregarding it but, for the latter, he accepts the studies without examination and then uses them to draw conclusions, again without explanation, far beyond what the studies themselves concluded. *See* § II(C) & (D), *supra*. Second, Dr. Van Stavern's reasons for disregarding the Norplant evidence are speculative and subjective; Dr. Van Stavern provides no basis for how the "inadequate documentation" renders the evidence useless, nor a reliable basis for how "confounding" by obesity would affect the weight data, much less render it useless. Third, whether or not a causal relationship has been "establish[ed]" between Norplant and IH, the Norplant data is still *relevant* to the question of whether Mirena is capable of causing IH, but Dr. Van Stavern improperly rejects the Norplant evidence entirely and does not incorporate it into his causal analysis.

C. In Contrast To Their Treatment Of The Norplant And Mirena Literature, Bayer's Experts Draw Sweeping Conclusions About Levonorgestrel From Literature Relating To Oral Contraceptives And IH That Never Evaluated Levonorgestrel Specifically, Which Did Not Adjust For Confounding At All, And Which, If Anything, Supported A Causal Association

Defendants' experts all support their opinions about Mirena and IH with conclusions about the lack of an association between "oral contraceptives" and IH, a conclusion supported by five studies: Digre 1984, Durcan 1988, Ireland 1990, Giuseffi 1991, Radhakrishnan 1993, all of which were either small studies with 1:1 or 1:2 case:control ratios or were "postcard surveys" of doctors in particular regions.[23] There are three independent problems with these opinions.

[23] Some of Bayer's experts, like Dr. Gossett, cite merely Ball 2006 as a "comprehensive review" that is "compelling for a number of reasons," that "number of reasons" apparently being two. *Report of Dr. Gossett*, p. 15. Ball 2006 devotes exactly one sentence to oral contraceptives and intracranial hypertension, a sentence which merely cites to Durcan 1988 and Ireland 1990. Such is plainly inadequate to support any conclusions.

First, all five studies addressed "oral contraceptives" in general, without any regard to levonorgestrel. As Ireland 1990 noted, "We could not contrast the oral contraceptive dosage or components, since half of both case and control subjects using oral contraceptives did not remember the brand used." Drawing conclusions about levonorgestrel from these studies is simply too great an analytical gap between the evidence and the conclusion. *See* § II (D), *supra*.

Second, Bayer's experts attempt to avoid the aforementioned by asserting that, in the 1980s and 1990s, several oral contraceptives included levonorgestrel. Yet, Bayer's experts never explain how they can use aggregated "oral contraceptives" to draw conclusions about oral contraceptives containing levonorgestrel, and, equally problematic, Bayer's experts never address how those same contraceptives that included levonorgestrel *also* included synthetic forms of estrogen, such as ethinyl estradiol. Comparisons between these oral contraceptives and Mirena, a levonorgestrel-*only* method, are inapt because estrogen substantially alters the clinical effects of levonorgestrel. Estrogen, *inter alia*, increases SHBG levels (and that SHBG then binds to levonorgestrel), interacts with androgen hormones and receptors, and interacts with steroids and the mineralocorticoid receptor—issues that Bayer's experts never even mention, much less address with a reliable scientific method, instead ignoring the issue. See § II (C) & (D).

Third, the primary reason Bayer's experts give for disregarding the published literature and the data relating to Norplant and Mirena is the possibility of "confounding," and the supposed need for patient-by-patient controlling for obesity and recent weight gain. Yet, not one of Bayer's eleven experts who rely on Digre 1984, Durcan 1988, Ireland 1990, Giuseffi 1991, or Radhakrishnan 1993 mentions that *none* of those studies controlled for confounding *at all*, much less on a patient-by-patient basis. All five studies merely performed a crude analysis of the frequency of oral contraceptive use among IH patients compared to controls, without attempting

any sort of adjustment or multi-variate analysis to incorporate obesity, overweight status, or recent weight gain, and, given the small sample sizes, none of the analyses came close to statistical significance.[24] Bayer's experts are thus trying to "have it both ways," are not applying a reliable method in a consistent manner, and are ignoring the limitations of the studies they rely upon, rendering their opinions inadmissible. See § II (C).

V. The Defendants' Experts Draw Broad Conclusions From Limited Data Without Explanation And Without Addressing Contrary Data, Then Rely On Those Unsupportable Conclusions For Their Overall Opinions

The four primary ways Bayer's experts attempt to avoid weighing the literature and data showing a causal association between Mirena and IH are: asserting "preferential prescribing" to obese women irredeemably confounds all case reports and case-control studies; "correcting" Valenzuela 2017 by radically raising the number of controls in the Mirena group while radically lowering the number of controls in the non-Mirena group; rejecting the dose-response relationship between levonorgestrel from Mirena and reports of IH; and, using the supposed *lack* of disproportionate adverse event reporting as evidence against a causal association. None of these conclusions withstand the scrutiny required by *Daubert*.

A. Bayer's Experts Do Not Have A Reliable Method For Concluding "Preferential Prescribing" Exists, Are Unable To Quantify Its Extent, And Refuse To Perform The Basic Analyses That Would Show If Preferential Prescribing Or Confounding By Indication Make Any Difference

All of Defendants' experts rely on "preferential prescribing" of Mirena to obese women, and thus potential "confounding by indication," as a basis for refusing to consider evidence

[24] Indeed, *four of those studies* found an increased use of oral contraceptives among patients with IH: in Digre 1984, 6/11 cases compared to 5/11 controls; in Durcan 1988, 17% of patients compared to 15.6% of the population; in Radhakrishnan 1993, an elevated odds ratio for IH of 1.39 (95% CI 0.63-3.04); in Ireland 1990, an elevated odds ratio for IH of 1.80 (0.42-7.64). In the remaining study, Giuseffi 1991, 20% of IH patients used oral contraceptives compared to 15% of controls, for an odds ratio of 0.6 (95% CI, 0.2-1.8).

suggesting a causal association between levonorgestrel and IH. There are two independent problems with these opinions.

First, the studies cited by Bayer's experts are not sufficient to conclude, with any degree of reliability, that Mirena is "preferentially prescribed" to obese women. None of the studies cited by Bayer's experts—e.g., Peipert 2011, Scott-Ram 2012, Saito-Tom 2015, Bhuva 2017, and Mosher 2017—concluded as much, and none even *addressed* the extent to which Mirena was prescribed to *anyone*. The only study with Mirena-specific data was Saito-Tom 2015, which made no effort to generalize about the public; rather, it was simply a review of continuation rates at a single clinic. Mosher 2017 used survey data *about intrauterine devices in general* to conclude that obese women were *not* statistically more likely to use an IUD, but Class II and III obese women were modestly more likely to use an IUD (12.7% of Class II or III obese women compared to 9.8% of underweight and normal-weight women). Bayer's experts never explain how or why they used these studies to conclude that Mirena users were more likely to be obese, much less substantially so, and instead made the leap that "preferential prescribing" might exist to some unspecified, unquantifiable extent, opinions which are impossible to evaluate objectively and are speculative, rendering them doubly inadmissible. *See* § II (B) & (D).

Second, *even if* "preferential prescribing" were a genuine phenomenon, Bayer's experts have not *applied* that supposed fact in any reliable manner to conclude that "confounding by indication" could impact the existing literature and data. Bayer's experts note that the incidence of IH among obese women is 22/100,000, compared to 6.8/100,000 among all women. But Defendants' never address how the vast majority of obese women (99,978/100,000) do *not* develop IH, and so "preferential prescribing" would have a minimal impact on studies.

The odds of an obese woman developing IH in any given year (1-in-4,545) are modestly

lower than the odds of being dealt a four-of-a-kind in Poker (1-in-4,164). Indeed, the odds of an obese woman developing IH in a given year are *lower* than the odds of a never-smoker in their 70s dying from lung cancer in a given year, but epidemiologists do not contend that an ≈25/100,000 annual death rate from lung cancer among never-smokers in their 70s is sufficient to conclude there is no increased risk of lung cancer from smoking.[25] The risk of IH among any population, including obese women of childbearing age, is so low that "adjusting" for factors like obesity will make little difference to the odds ratio in a case-control study. Although an "adjustment" of this sort would be trivial to do, such as adding another "stratum" to a 2x2 table to reflect the supposed preferential prescribing, none of Bayer's experts attempted to do so, and instead have proffered the subjective, conjectural opinion that there is sufficient "confounding by indication," measured in a purely subjective fashion, that they can disregard the literature and data entirely.[26] Such opinions are speculative and impossible to evaluate objectively. *See* § II (B) & (D).

B. Bayer's Experts Cannot Justify The "Corrections" They Make To Valenzuela 2017

Remarkably, all of Bayer's neuro-ophthalmologists, OBGYNs, and epidemiologists analyzed the Valenzuela 2017 paper the same way and concluded, with the same sources, that it would be proper for them to reject Valenzuela's peer-reviewed analysis and "correct" it.

In the Utah portion, Bayer's experts arbitrarily moved 17,682 women from the non-Mirena control group to the Mirena control group, thereby substantially lowering the odds ratio.

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[25] Samet, et al., Lung Cancer In Never Smokers, Clin Cancer Res. 2009 Sep 15; 15(18): 5626–5645.

[26] The Court can perform this analysis itself, using OpenEpi's 2x2 table and adding a second stratum. Even making the absurd assumption that 100% of the Mirena users in the Utah portion of Valenzuela 2017 were obese, whereas the non-Mirena users reflected the normal population, still produces an odds ratio of 5.308 (95% confidence interval 3.022, 9.325) for IH among Mirena users.

The justification for this "correction"—a blatant numbers-fixing method unsupported by any literature cited by any of Bayer's experts, in which the actual University of Utah Mirena billing data used by Valenzuela was discarded—was an estimate that 10% of women in Utah use Mirena.

The "method" behind this 10% estimate is a convoluted five-step process that mixes together four surveys and an analysis of the same University of Utah billing database that Valenzuela 2017 used and Bayer's experts rejected. The supposed calculation multiplies together the percent of women aged 18-44 in Utah at risk for unintended pregnancy who used a LARC (Boulet 2016), the percent of women nationwide at risk for unintended pregnancy who did not use contraception (Jones 2012), the percent of all women aged 15-44 nationwide who used a LARC (Branum 2015), the percent of women nationwide who used an IUD (Kavanaugh 2015), and the percent of women at the University of Utah aged 15-44 who had Mirena implanted as compared to another IUD (Sanders 2017, Sanders also being a co-author of Valenzuela). This "method" is a classic opinion "so unrealistic and contradictory as to suggest bad faith or to be in essence an apples and oranges comparison,"[27] and it should be precluded on that basis alone.

Unsurprisingly, none of Bayer's experts actually performed the calculation in their report. At the very most, they cited numbers from Boulet 2016, Branum 2015, and Sanders 2017, studies which together simply will not produce the desired result, because they mix together data on women "at risk for unintended pregnancy" (via Boulet 2015) and data for *all* women (via Branum 2015 and Sanders 2017). At deposition, Dr. Barnhart revealed how Jones 2012 was used, and the math swiftly fell apart: the calculation required assuming that the 17% of women nationwide identified by Jones 2012 as using "female sterilization" were somehow also "at risk

[27] *Boucher v. U.S. Suzuki Motor Corp.*, 73 F.3d 18, 21 (2d Cir.1996).

for unintended pregnancy." Dr. Barnhart admitted that using Jones 2012 was "trying to match, proverbial, you know, round pegs in square holes or whatever the analogy is," 99:18-101:7, and so he tried to rely on Kavanaugh 2015, saying "the data I got was from a table," 101:8-102:8, but, even with the benefit of a lunch break to review the papers, he admitted Kavanaugh 2015 would not fix the problem and he "didn't use it to actually arrive at my calculation." 105:23-106:19.

Not one of Bayer's experts has justified their use of the "10%" estimate for Mirena use in Utah, much less their "correction" of Valenzuela 2017, much less their rejection of Valenzuela 2017, and they should all be precluded from testifying about these issues. *See* § II (B), (C) & (D).

The similar "correction" Bayer's experts performed on the Denmark portion of Valenzuela 2017 should also be rejected. The *sole* basis for "correcting" the Mirena usage numbers[28] is Lindh 2016, a "pure descriptive assessment" of *relative* contraceptive use that made no effort to reflect *absolute* contraceptive use among the population, and which calculated Mirena use by aggregating prescription data and arbitrarily setting "the mean duration of use" to be four years. As Plaintiffs' expert Dr. Moye noted, and none of Bayer's experts addressed, attempting to apply the Lindh 2016 as a reflection of *absolute* Mirena usage produces an absurd result in which there were nearly three times as many Mirena prescriptions in 2013 as there were sales in 2014. None of Defendants experts addressed these issues, rendering these opinions and the opinions based upon them inadmissible. *See* § II (B), (C) & (D).

C. Bayer's Experts Claims About Levonorgestrel Serum Levels Are Baseless

One factor in assessing causation under Bradford Hill is the presence of a dose-response

[28] As with the Utah "correction," the "correction" to the Denmark data by Bayer's experts simply moved 10,021 from the non-Mirena controls to the Mirena controls, thereby significantly lowering the odds ratio. Such is not a reliable method recognized by any literature.

relationship. As several of Plaintiffs' experts note, Bayer's own adverse event data shows that most IH cases with information about the timing of diagnosis occurred within the first two years after Mirena placement, which corresponds to the period in which LNG levels are highest and most variable. The Prescribing Information for Mirena says:

> A stable serum concentration, without peaks and troughs, of LNG of 150–200 pg/mL occurs after the first few weeks following insertion of Mirena. LNG concentrations after long-term use of 12, 24, and 60 months were 180±66 pg/mL, 192±140 pg/mL, and 159±59 pg/mL, respectively.

Rather than address this data, all of Bayer's experts[29] make a contrary assertion (typically with suspiciously similar wording[30]) that LNG levels are at their highest in the first few months and then steadily decline, and then use that assertion as a justification for claiming the data is inconsistent with a dose-response relationship. Bayer's experts cite one of two sources for this claim: the Mirena Prescribing Information (which does not support it) and Apter 2014, a study by Bayer employees that *also* found serum levels were highest in the first two years, and which cannot be read to support the claim by Bayer's experts that LNG levels are somehow substantially different "in the first few months."[31] These opinions are contrary to the materials cited, are unsupported by any method that can be objectively evaluated, and are purely

[29] The exception is Dr. Jusko, the only pharmacologist among Bayer's experts, who does not make this particular assertion, but whose opinions are flawed for other reasons, as explained in his brief.

[30] Dr. Gossett, p. 24 (LNG serum levels "are highest in the first few months after placement, drop off, then decline over time."); Dr. Cestari, p. 21 (LNG serum levels "are highest in the first few months after insertion and decline steadily thereafter…"); Dr. Hewitt, p. 22 (LNG serum levels "are highest in the first few months of release and declines thereafter…"); Dr. Van Stavern (LNG serum levels "highest shortly after insertion and decline steadily thereafter…"); Dr. Rizzo, p. 17 (LNG serum levels "highest in the first months after insertion…"); Dr. Barnhart, pp. 54-55 (LNG serum levels "highest in the first few months after insertion and declines thereafter…"); Dr. Lee, p. 32 (LNG serum levels "highest in the first few months of insertion and declines thereafter").

[31] Apter 2014 also said, "The main limitations of the study are the relatively low number of subjects evaluated in the detailed PK and PD analyses, which makes interpretation of the results difficult, and the fact that this was an analysis of subgroups from the phase II and III studies." None of Bayer's experts made any effort to address these limitations.

speculative, rendering them in admissible. *See* § II (B), (C) & (D).

D. Bayer's Experts Improperly Attempt To "Have It Both Ways" With Adverse Event Disproportionality, And Bayer Withheld From Its Experts Critical Data About Adverse Event Disproportionality

Defendants' experts recognize "the FDA has affirmatively recognized the dangers of relying on [adverse event disproportionality] studies for causal assessments," *Report of Dr. Gossett*, p. 17,[32] but then, inexplicably, they use those same adverse event disproportionality studies to "support a *lack* of association between Mirena use and IIH," p. 18 (emphasis in original).[33] There are three problems with these analyses.

First, it is difficult to imagine a *less* reliable method than one in which an expert admits upfront that certain data should not be used a certain way and then proceeds to use that data in that way. Either adverse event disproportionality studies can be used in causal assessments or they cannot; there is no logical, much less reliable and scientific, way to do both. *See* § II (C).

Second, Defendants' experts are cursory, subjective, and made without reference to any literature supporting their methods, such as by absurdly comparing the *rate at which adverse*

[32] See also Report of Dr. Cestari, p. 16; Report of Dr. Rizzo, p. 11; Report of Dr. Barnhart, p. 10; Report of Dr. Newman, p. 9; Report of Dr. Langer, p. 8; Report of Dr. Lee, pp. 3-4, 11;

[33] See also Dr. Van Stavern, p. 15 (relying on "no signal for IIH in adverse event reporting" to justify not performing a Bradford Hill analysis); Dr. Rizzo, p. 14 (relying on "reporting rate" of adverse events as evidence against "the conclusion that Mirena plays a causal role in IIH"); Dr. Barnhart, pp. 50-56 (relying on Bayer's adverse event signal assessments to conclude "there is no increased risk of IIH associated with the use of LNG IUS."; Dr. Newman, p. 9 (opining that reduced reporting "does not support a causal relationship") and p. 10 (opining that "rate of case reports … below the expected rate" is evidence contrary to causal relationship); Dr. Langer, p. 24 (relying on adverse event reporting as not "support[ing] a relationship between Mirena and IIH") and p. 37 (relying on "reporting frequency" of adverse event reports as evidence not supporting causal association) and p. 40 (asserting "disproportional reporting" is relevant to "evidence [of] a true association between Mirena and IIH") and p. 41 (adverse event "reporting rate" is evidence "that there is no meaningful association"); Dr. Lee, pp. 26-33 (using "signal detection studies" and "a disproportionality analysis" as part of "the evidence evaluating a potential association between Mirena and IIH"); Dalton, p. 19 (relying on adverse event signal analysis as "show[ing] no relationship" between Mirena and IIH)

events are reported to the *rate of the disease in the population*, a method explicitly rejected by the FDA, which emphasizes that adverse event reporting can never be directly compared to the population as a whole given that the extent of underreporting is unknown, as is the denominator.[34]

Third, although virtually all of Bayer's experts opine on "signal detection" and "adverse event disproportionality," not one of Bayer's experts was provided with Bayer's own internal disproportionality analyses. Such is not surprising: Bayer did not provide it to Plaintiffs, either, and removed every single reference to it from their document productions, despite their representations to the Court[35] and the agreed-upon ESI protocol and search terms. The existence of Bayer's Empirica database was only revealed at the deposition of Bayer's pharmacovigilance designee, Dr. Schoendorf, when confronted with the absence of any disproportionality analyses, which is contrary to FDA Guidance.[36]

At Bayer, the threshold for disproportionate adverse event reporting is to have more than 3 cases, a proportional reporting ratio (PRR) of 2 of more, and a Chi^2 of 4 or more.[37] As of August 1, 2014, which is as far back as Defendants provided the Empirica data, Bayer's own signal detection database showed for IH and Mirena 41 cases, a PRR of 3.883, and Chi^2 of

[34] FDA Guidance For Industry, Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, p. 11: "for spontaneously reported events, it is not possible to identify all cases because of under-reporting, and the size of the population at risk is at best an estimate."

[35] July 27, 2017 conference, p. 43: "[w]e specifically talked to [Dr. Schoendorf] to make sure we gather all the data that went into her signal assessment, to produce that as well. And I think that leaves no dispute."

[36] FDA Guidance, *ibid*, p. 11: "we recommend that sponsors calculate crude adverse event reporting rates as a valuable step in the investigation and assessment of adverse events."

[37] Deposition of Katrin Manlik, 22:17-23:2; see also Candore, et al., *Comparison of statistical signal detection methods within and across spontaneous reporting databases*, Drug Saf. 2015 Jun;38(6):577-87. (Co-authored by Katrin Manlik, listing same criteria for Bayer in Table 2.)

52.995. As of December 1, 2017, the cases were 440, the PRR was 44.456, and the Chi^2 was 3,224.846. Bayer's expert epidemiologist Dr. Langer was not provided the Empirica figures, and he admitted a PRR greater than 40 would "certainly" support causation, that he "[has] never seen a Chi^2" greater than 3,000, and that it "would be consistent with a causal association." *Deposition of Dr. Langer*, 188:2-189:22. It is no mystery why Bayer did not provide the Empirica data to their experts: it directly contradicts their opinions. That failure renders their opinions on disproportionality, and the causation opinions the experts made in reliance on them, inadmissible. *See* § II (C).

VI. Bayers' Experts Claim Expertise In The Mechanisms Of Levonorgestrel and The Pathophysiology Of IH But Then Provide Only Cursory And Error-Laden Reviews Of Plaintiffs' Experts' Reports, And No Review Of Literature Or Data

The experts disclosed by Plaintiffs include a world-renown researcher of intracranial hypertension (Dr. Salpietro), a world-renown researcher of cerebrospinal fluid dynamics (Dr. Johanson), and the preeminent OBGYN clinical researcher in the United States, who is currently leading a clinical trial on Mirena for Bayer (Dr. Darney). Their opinions will be discussed more fully in response to Defendants' *Daubert* motions. For purposes here, the issue is the cursory attention Bayer's experts paid to their reports. Bayer's experts have responded to these reports by ignoring the literature and data cited by Dr. Salpietro, Dr. Johanson, and Dr. Darney, and by stating outright falsehoods, such as this claim by Dr. Dalton: "[t]he contemporary consensus within the published literature is that the previously hypothesized relationship between sex hormones and IIH has been disproven by controlled studies." *Report of Dr. Dalton*, pp. 32-33. There is no such "consensus"—the "consensus" is the opposite, and there are no "controlled studies" with the objective of causing IH, because such studies would be blatantly unethical—and even Bayer's own corporate designee for pharmacovigilance, Dr. Juliane Schoendorf, admitted "it is a valid hypothesis to investigate further whether there is influence of sex

hormones on the development of IIH." *Deposition of Dr. Schoendorf*, 100:10-22.

Bayer's experts have simply refused to review the literature and data presented to them by Dr. Salpietro, Dr. Johanson, and Dr. Darney, and their cursory, inaccurate criticisms do not demonstrate an objective method being used, rendering them inadmissible. § II (B) & (C).

VII. Conclusion

Bayer's experts apply non-existent, or flawed methodology in response to Plaintiffs' experts. Their analyses are the product of unscientific advocacy and cannot pass *Daubert* muster. Individually and collectively, Bayer's experts suffer numerous methodological shortcomings and logical errors in the application of unfounded assumptions. Their opinions are therefore unreliable and inadmissible under Rule 702 and *Daubert* and must be excluded.

For the foregoing reasons, and those detailed in each of Plaintiffs' Memoranda in Support for their individual Motions to Exclude the General Causation Testimony of Bayer's expert witnesses, Plaintiffs' respectfully ask this Court to grant their Motions and exclude the testimony of Bayer's general causation expert witnesses.

Dated: March 2, 2018

Respectfully submitted,

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that the foregoing was filed via the ECF/CM system with the Clerk of the Court, which will have sent notice to all attorneys of record in this matter on March 2, 2018.

/s/ *Maxwell S. Kennerly*
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